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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/026,931	MAHLER ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-34,37-41,43-46 and 48-54* is/are pending in the application.

4a) Of the above claim(s) *24-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *33,34,37-41,43-46 and 48-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 29, 2007 has been entered.

Applicant's response and amendments received January 27, 2007 are acknowledged.

Claims 1-23, 35, 36, 42 and 47 have been canceled.
Claims 33, 34, and 37 have been amended.
Claims 24-34, 37-41, 43-46 and 48-54 are pending in the instant application.
Claims 24-32 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the office action mailed May 20, 2005.

Claims 33, 34, 37-41, 43-46 and 48-54 are under examination in this office action as they read on methods of treating IgE-mediated allergic disorders by administering allergen derivatives.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 53 and 54 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record.

The office action mailed November 27, 2006 states:

> Specifically, these claims recite specific length fragments of Bet v 1, yet the specification does not provide a sequence for Bet v 1. Many Bet v 1 sequences are known in the art, and these sequences differ in amino acid composition and in length (Friedl-Hajek et al., Molecular Immunology, 1999, 36:639-645, see entire document particularly Figure 1). As such, defining a fragment of Bet v 1 as being, for example, amino acids 1-73, without recitation of a single specific reference sequence for Bet v 1 renders the claim indefinite since the metes and bounds of the administered allergen derivatives are not clear.

Applicant has acknowledged that this rejection is of record (see page 7 of the response entered January 29, 2007) but no rebuttal to this argument appears to be included with applicant's response.

As such, it appears that applicant agrees with the examiner's analysis of the claimed invention. The rejection is maintained.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 33, 34, 37-41, 43-46 and 48-54 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the recitation of new matter has been withdrawn in view of applicant's claim amendments received January 27, 2007.

Specifically, applicant has amended the instant claims in a manner that is supported by the instant specification, including passages such as the third full paragraph of page 2 and paragraphs 3-5 of page 4 of the instant specification. Note that the specification specifically discloses how "allergenic activity" is to be determined in the third paragraph of page 4. As such, the claims as amended do not recite new matter.

6. Claims 33, 34, 37-41, 43-46 and 48-54 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating birch allergy by administering trimers of Bet v 1, administering amino acid fragment 1-73 of Bet v 1, or amino acid fragment 74-159 of Bet v 1, does not reasonably provide

enablement for the treatment or prevention of alder, birch, and hazel allergy by administering generic derivatives of the major allergens of alder, birch, and hazel. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has broadly claimed a method of treating or preventing IgE-mediated allergic disorders resulting from exposure to the major allergens of alder, birch and hazel by repeatedly administering derivatives of a major allergen of alder, birch, or hazel. To support such methods, applicant has disclosed an in vivo model wherein trimers of Bet v 1, amino acids 1-73 of Bet v 1, and amino acids 74-159 of Bet v 1 are administered to mice such that the mice generate an antibody response that blocks the binding of IgE from birch pollen allergic patients to native Bet v 1 allergen (see particularly Examples 2 and 5).

Applicant's claimed invention recites methods of treating or preventing an IgE-mediated allergic disorder, but the specification does not appear to define the term prevent. Allergic reactions occur subsequent to allergen reexposure, and as such one reasonable interpretation of "prevention" is that therapy needs to be initiated prior to rexposure to the allergen such that the development of an allergen specific IgE response never occurs. Another reasonable interpretation of "preventing" is that the therapeutic method is 100% effective in 100% of patients.

The development of an allergen specific IgE response is due to the complex interplay of environmental and genetic factors, and therefore it is not predictable who will or will not develop an allergic response to a given allergen (Blumenthal et al., chapter 2 of Allergens and Allergen Immunotherapy, third edition, 2004, pages 37-50, see entire document particularly pages 42-46, Figure 2, and the salient points section spanning pages 47 and 48). The claims recite that the allergen derivative is to be administered to a patient in need thereof, but as discussed above it is unpredictable who will or will not develop an IgE-mediated disorder specific for a given allergen. As such the only identifiable patients in need of treatment are those already known to suffer from allergies specific for a given allergen. These patients currently have an ongoing

IgE-mediated immune response directed to the specific allergen, and as such the IgE-mediated reaction cannot be prevented because it has already occurred. Given the unpredictability in who will or will not develop an allergic reaction as taught by Blumenthal et al., it is unlikely that any specific therapy will be effective in all patients. Additionally, while it is known that epitope crossreactivity is common among alder, birch and hazel pollen allergens, unique epitopes can be found that are not present in the genus of all Fagales (which includes birch, alder, and hazel) pollens and as such crossreactivity of a derivative is not guaranteed (Breiteneder et al. and Bohle et al., see entire documents). Further, specific immunotherapy is not effective in all patients, and even when treatment is clinically effective, the majority of patients demonstrate decreased severity of IgE mediated disorders, rather than the prevention and complete cessation of IgE-mediated disorders (Norman, PS, see entire document particularly the paragraph spanning pages 681 and 682, and Malling HJ, see entire document, particularly page 497).

Applicant's claimed method is also broad in that the independent claim recites a method wherein an agent is administered to a patient, wherein the agent is identified via a screening assay that selects agents which comprise the functional properties of inducing an IgE-blocking antibody response and comprise reduced allergenic activity as compared to the native allergen. On page 4, the specification discloses:

"According to the invention the allergenic activity of a sample is determined by determining the IgE antibodies which are induced in a test animal upon application of the sample. The allergenic activity is preferably defined in suitable in vitro or in vivo tests. A preferred in vitro test is the basophil histamine release assay as described in Vrtala et al., J. Clin. Invest. 1997, 99, pp. 1673-1681. Alternatively the allergenic activity is determined in a skin test as described in van Hage-Hamsten et al. J. Allergy Clin. Immunol. 1999, 104, pp. 969-977 or in Pauli et al. Clin. Exp. Allergy 2000, 30, pp.1076-1084." As such it appears that the screening methods to be used to determine "allergenic activity" are known in the prior art.

The specification further discloses that the administered agent is a derivative of a naturally occurring allergen, and in the paragraph spanning pages 2 and 3, it is

disclosed that derivatives of an allergen can be fragments, oligomers, and chemically modified forms of naturally occurring allergens as well as molecules obtained by site directed mutagenesis of an allergen protein.

Polypeptide derivatives of specific allergens are known in the art, and applicant has provided examples of three derivatives of Bet v 1, namely a trimer of Bet v 1, the polypeptide consisting of amino acids 1-73 of Bet v 1, and the polypeptide consisting of amino acids 74-159 of Bet v 1 to support the claimed invention. All three of these derivatives are known to comprise decreased allergic activity as measured by histamine release and skin prick testing as disclosed by Valenta et al. (WO 99/16467, of record, see entire document).

However, there currently is no art recognized method to distinguish allergic from non-allergic molecules (such as derivatives comprising fragments and oligomers of allergens) on an a priori structural basis (Blumenthal et al., see particularly the last sentence of the third complete paragraph of page 39). If the identity of the IgE binding epitopes that give rise to the allergic activity of an allergen are precisely known, it is not predictable as to which amino acid positions within an epitope need to be altered by site directed mutagenesis such that IgE binding is abrogated (Burks et al., Eur. J. Biochem., 1997, 245:334-339, see entire document, particularly the top right column of page 338). Even when a precise amino acid within in the epitope to be altered is identified, the choice of what that amino acid should be mutated to by site directed mutagenesis is not predictable since some substituted amino acids reduce IgE binding while others have no effect or unexpectedly increase IgE binding (Nishiyama et al., US Patent 6,187,311, see entire document, particularly lines 4-30 of column 3, and Reese et al., J. Immunol., 2005, 175:8354-8364, see entire document, particularly the paragraph that spans pages 8357 and 8358, Table I and Figure 2). The specification does not appear to teach what changes are to be made in naturally occurring allergens to make derivatives that satisfy the recited functional criteria, and the teachings of the art indicate that the structure of the material obtained as an immunotherapeutic agent comprising reduced allergenic activity at the conclusion of a screening protocol cannot be predicted. Given the above, it appears that a skilled artisan would need to rely on trial and error to identify

derivatives suitable for use in the recited method. Trial and error by definition is random and unpredictable, and therefore a skilled artisan would need to perform an undue amount of research prior to practicing the full breadth of applicant's claimed method.

Therefore, given the breadth of the instant claimed invention, the amount of guidance and working examples disclosed in the specification, and the teachings of the art, a skilled artisan would be unable to practice the full breadth of applicant's claimed invention without conducting an undue amount of additional research.

Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant's first argument is that the claims have been amended such that they only read on the treatment and prevention of IgE mediated disorders that result from exposure to alder, birch, or hazel allergens in patients allergic to alder, birch and/or hazel pollen and do not read on the treatment and prevention of all IgE-mediated disorders.

This argument is not persuasive because as is explained supra the allergic epitopes which mediate allergy to alder, birch, and hazel pollen are not coextensive such that administration of a derivative of any one allergen of one tree pollen would necessarily be effectively crossreact with all major allergens of alder, birch, and hazel.

Applicant also argues that prevention means avoiding the symptoms of a disorder and thus does not require 100% effectiveness.

This argument is not convincing because the definition of prevention as argued by applicant does not appear to be disclosed by the instant specification. Further, applicant has not supplied evidence that supports the argued definition of prevention. Applicant is reminded that as per MPEP 2145:

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
>
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of

obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

Applicant also argues that while some trial and error may be required to practice the instant claimed invention, the requisite level of experimentation is not undue. Specifically, "the current invention is most aptly described as heuristic and leads quickly, without under experimentation to the identification of candidate immunotherapeutic agents even though some trial and error might be involved. Unlike the classic methodology, the instant methodology is not so concerned about the structure of the derivative as it concerned that the derivatives are therapeutic candidates. It is the position of the invention that a derivative may be generated by any means known, expedient, and undue, and as such sees no purpose in burdening the specification with what is readily available in a standard biotechnology laboratory manual. It is the position of the invention, however, that it takes a very simple trial to determine whether the derivative is a candidate therapeutic agent and if it is, said derivative may be used as such without ever trying to determine its exact molecular structure. The claims set only two criteria namely: whether the derivative (of whatever structure) induces IgE-blocking antibodies in vivo and has substantially diminished allergenic activity. The claims then go one step further to teach how to use these derivatives (of whatever structure) to treat causally related IgE-mediated allergic disorders." As such, applicant argues that the specification enables the therapeutic administration of agents identified via a screening assay even when the agents identified by the screening assay are as of yet unknown.

This argument is not persuasive. While the specification may disclose a screening method, the derivatives identified by such a method (excepting the three disclosed derivatives discussed supra) are not disclosed. The instant claims are designed to cover the administration of such derivatives prior to identification of the derivatives themselves. In order to satisfy 35 U.S.C 112, 1st paragraph, the specification has to teach how to make and use the invention, not how to screen to identify the invention. Until the time when the derivatives administered as part of the

claimed method are identified, a skilled artisan would not know how to make, and thus could not use, such a derivative in the instant claimed method.

The rejection is maintained.

7. Claims 33, 34, 37-41, 43-46, and 48-51 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The office action mailed June 20, 2006 states:

> Applicant has claimed a method of treating or preventing IgE-mediated allergic disorders by repeatedly administering an agent to a patient, wherein the agent is a derivative of a naturally occurring allergen that has been selected via a screening protocol to identify derivatives that induce a blocking antibody response and that exhibit decreased allergen specific IgE binding as compared to the wildtype allergen. In support of the genus of administered agents that are allergen derivatives, applicant has provided three examples concerning the birch pollen allergen Bet v 1, namely a trimer of Bet v 1, the polypeptide consisting of amino acids 1-73 of Bet V 1 or the polypeptide consisting of amino acids 74-159 of Bet v 1. This disclosure does not support the claimed genus for the reasons set forth below.
>
> The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).
>
> As discussed at length in paragraph 8 of this office action, the disclosed trimer of Bet v 1 does not comprise all of the recited functional properties, and as such it is not part of the recited genus of allergen derivatives. The two fragments of Bet v 1 do comprise all of the functional properties, but the independent claim is not limited to these particular fragments, or even to the birch pollen allergen Bet v 1. The recited genus of grass pollen allergens is very large and structurally diverse (see particularly chapter 11 of Lockey et al.), and applicant has defined derivatives in the paragraph spanning pages 2 and 3 of the specification to be fragments, oligomers, and chemically modified forms of naturally occurring allergens as well as molecules obtained by site directed mutagenesis of an allergen protein. The structure of these derivatives is not taught, and while functional properties are recited, the specification does not teach how these functional properties are correlated with structure. Further, the art teaches that correlations between structure and IgE binding (or the lack of IgE binding) cannot be predicted on an a priori structural basis (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages 37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39). As such, the disclosure of the polypeptides consisting of amino acids 1-73 and consisting of amino acids 74-159 of Bet v 1 do not comprise a representative number of species to support the recited genus of grass pollen allergen derivatives, and thus the recited genus lacks written description.

The office action mailed November 27, 2006 states:

> Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant argues that the specification does provide written description for derivatives of the wild type allergens of alder, hazel and birch because all of these "derivatives" have the functional property of

eliciting IgE-blocking antibodies and that "this identifying characteristic, without more, has given possession to the applicants, as of the filing date" the instant claimed methods.

This argument is not persuasive. As previously stated:

> The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

As discussed in the prior office action, the specification does not disclose a representative number of species that comprise the genus of derivatives of all birch, hazel and alder allergens, nor does it disclose a structure common to said derivatives. The disclosure of a functional characteristic, namely eliciting IgE-blocking antibodies, is made without a disclosed correlation between this functional characteristic and structure. As such, in the absence of more, applicant was not in possession of the genus of allergen derivatives recited for use in the instant claimed methods at the time the instant application was filed.

Note that in The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court held that disclosure of a single member of a genus (rat insulin) did not provide adequate written support for the claimed genus (all mammalian insulins), and that the genus of all mammalian insulins is more structurally similar than the genus comprising all derivatives of all allergens of birch, hazel and alder. In this same case the court stated, "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene ("derivative") does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes ("derivatives") may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Therefore, it appears that the broad genus of allergen derivatives recited in the instant method claims lacks adequate written description because there does not appear to be any correlation between structure and function excepting the working examples concerning the two fragments of Bet v 1 disclosed in the specification as having been made by Vrtala et al. in their 1997 J. Clin. Invest. paper. As such a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of allergen derivatives at the time the instant application was filed.

Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant argues that "The written description requirement has been met in this case by disclosure of relevant identifying characteristics - namely that the candidate therapeutic agents of this invention are those which upon injection into an immunological model elicit both IgE-blocking antibodies production and also have reduced allergenicity compared to wild-type allergens. This identifying characteristic, without more, has given possession to the Applicants, as at the filing date, of treatment

methods using the results of the elegant in vivo screening methodology of the present invention."

This argument is not persuasive because the instant specification does not disclose how the structure of the derivative is correlated with the functional properties of eliciting IgE-blocking antibodies and reduced allergenicity. Even if a skilled artisan could obtain derivatives using a screening assay, the structure of derivatives that comprise the desired functional properties would not be known until such time as the screening assay is completed. How can the specification provide adequate written description for a derivative that cannot be known until the completion of a screening method that has yet to be performed? Note that in Univ. of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (Fed.Cir. 2004) the court held that the disclosure of a screening assay and the recitation of functional properties of molecules obtained upon completion of said screening assay did not provide adequate written description for the molecules themselves. More specifically, the court held that patented claims which encompassed methods of treatment with undiscovered Cox-2 inhibitors such as Celebrex were invalid for lack of possession of the genus of administered Cox-2 inhibitors.

The instant case is similar in that the specification provides a screening assay and recites functional properties of allergen derivatives that are yet to be discovered. Further, the three Bet v 1 derivatives that are disclosed (trimer, amino acids 1-73 and amino acids 74-159) are not representative species of the genus of all major allergens of alder, hazel, and birch.

Note that applicant's amendment to independent claim 33 has removed claim 51 from the rejection of record because trimers of Bet v 1 comprise reduced "allergenic activity" as per the meaning of "allergenic activity" disclosed on page 4 of the instant application.

The rejection is maintained.

Claim Rejections - 35 USC § 102/103

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 33, 34, 37-40, 43-46, 48, 49, 51, 53 and 54 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, of record, see entire document).

Vrtala et al. teach methods of specific immunotherapy to treat birch allergy by administering derivatives of Bet v 1 (see entire document, particularly the abstract and the left column of page 6658). The administered derivatives induced the production of antibodies which precluded the binding of IgE antibodies to native Bet v 1 allergen (see particularly the abstract and Tables II-IV). The derivatives of Bet v 1 are taught as being repeatedly administered at the same concentration at intervals greater than 14 days, with such administrations occurring four times (see particularly the second and third paragraphs of the right column of page 6654). Administered dosages are taught as

comprising 5 μg and 200 μg of Bet v 1 derivatives (ibid.). These dosages are further taught as being adsorbed onto an adjuvant (ibid. and the last sentence of the first full paragraph of the left column of page 6658).

It is noted that the Bet v 1 derivatives of Vrtala et al. were administered to model organisms, namely mice and rabbits. However, given their disclosure that the Bet v 1 derivatives are to be used for immunotherapy and that clinical trials are to be conducted, a skilled artisan would immediately envisage administering the Bet v 1 derivatives to humans. Alternatively, a person of ordinary skill in the art would have been motivated to administer the Bet v 1 derivatives to humans because Vrtala et al. specifically disclose that their derivates are to be used for immunotherapy, comprise advantageous properties such as reduced side effects, and that they are planning a clinical trial involving the administration of their derivatives (see particularly the two full paragraphs of the left column of page 6658). As such, administering the derivatives to humans is merely doing what Vrtala et al. plan to do but have not yet done. A person of ordinary skill in the art would have a reasonable expectation of success in treating humans based on the success of the method in two distinct animal models, namely mice and rabbits.

Note that claims 53 and 54 recite administering peptides consisting of amino acids 1-73 or 74-159 of Bet v 1. The specification indicates on page 8 that the recombinant Bet v 1 fragments used in the instant specification are the peptides disclosed in the 1997 J. Clin. Invest. article by Vrtala et al. In this 1997 article, Vrtala et al. teach how to make recombinant Bet v 1 fragments consisting of amino acids 1-74 and 75-160 of Bet v 1. Note that the 2000 J. Immunology paper by Vrtala et al. that forms the basis of this rejection discloses the use of Bet v 1 fragments consisting of amino acids 1-74 and 75-160, and references the 1997 J. Clin. Invest. paper in the materials and methods section for details concerning the manufacture of said peptides. As such, it appears that the Bet v 1 fragments taught in the prior art and those used in the instant specification are the same fragments with the discrepancy between the amino acid numbering being a typographical error of the instant specification.

Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant's argues that "the Vrtala publication is at best a mere experimental disclosure of certain aspects of the present invention and does not enablingly disclose the invention as claimed" because the reference does not teach a working example of treating humans.

This argument is not persuasive because as discussed above, Vrtala et al. specifically teach that their Bet v 1 derivatives are to be taught for use in specific immunotherapy, that several advantages, such as reduced side effects, are anticipated to gained by using their derivatives for immunotherapy, and that clinical trials of their derivatives are planned. As such, a skilled artisan would readily envisage applying the disclosed treatment methodology to humans and would expect it to work given that the same methodology was successfully used in two distinct in vivo model systems, namely mouse and rabbit.

Applicant also argues that the instant claimed method is not anticipated because claim 33 and its dependent claim have a "periodicity element" which is essential to successful immunotherapy and that "the Vrtala reference cannot reasonably be said to have sufficiently disclosed, to a patentably enabling detail, the periodicity element claimed in the invention which is very vital to a successful immunotherapy."

This argument is not persuasive because Vrtala et al. teach monthly injections, thus satisfying all recited periodicity elements of the claims indicated as rejected. Specifically, monthly injections, such as those disclosed by Vrtala et al., mean that the "period between administrations is at least 14 days" and immunizations occurred 4 times (see particularly the right column of page 6654).

Additionally, applicant is reminded that the only working examples present in the instant specification to demonstrate enablement comprise repeated administrations of Bet v 1 derivatives to mice, not humans. As such, applicant appears to argue for a double standard, holding the teachings of the prior art to a higher level of enablement that what is found in the instant specification. The courts have examined this issue, and in cases such as *Rasmusson v. SmithKlein Beecham Corp.*, 75 USPQ2d 1297 (CAFC 2005), it is stated:

> "The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. In *In re Hafner*, 410 F.2d 1403 [161 USPQ 783] (CCPA 1969), the court stated that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim." *Id.* at 1405; *see Schoenwald*, 964 F.2d at 1124; *In re Samour*, 571 F.2d 559, 563-64 [197 USPQ 1] (CCPA 1978). The reason is that section 112 "provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure." *Hafner*, 410 F.2d at 1405; *see* 1 Donald S. Chisum, *Chisum on Patents* §3.04[1][c] (2002); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349-52 [64 USPQ2d 1202] (Fed. Cir. 2001) (finding anticipation where applicant sought a patent based on a new use for a previously disclosed method)."

As such, applicant's arguments that the prior art is not enabled is not persuasive.

Finally, applicant has not commented on the apparent nomenclature discrepancy between the prior art and the instant specification concerning the specific amino acids of Bet v 1 that comprise the allergen derivatives that are administered by the recited method. Given that applicant has not commented on this issue, it appears that applicant agrees with the examiner's analysis that the instant specification comprises an inadvertent typographical error and thus claims 53 and 54 are properly included in this rejection.

11. Claims 33, 34, 37, 46, and 48-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenta et al. (WO 99/16467 A1, of record, see entire document) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, see entire document).

Valenta et al. teach a method of treating birch allergy by repeatedly administering derivatives of Bet v 1 (see entire document, particularly the abstract and the paragraph spanning pages 5 and 6 and claims 11-16). The Bet v 1 derivatives comprise the polypeptides consisting of amino acids 1-74 of Bet v 1 and amino acids 75-160 of Bet v 1, as well as trimers of Bet v 1 (see particularly lines 9-34 of page 4, Example 1 from

pages 6-13, most particularly lines 16-37 of page 13, and Example 3 from pages 15-19, most particularly lines 10-13 of page 19). These polypeptides are taught as being combined with the pharmaceutically acceptable adsorbate and adjuvant aluminum hydroxide prior to *in vivo* administration (see particularly lines 2-9 of page 6). The trimers Bet v 1 derivatives of Valenta et al. give at least 10-fold reduced reactions in skin prick tests of allergic individuals while the fragments of Bet v 1 do not appear to comprise any allergenic activity (see particularly lines 3-14 of page 13 and lines 10-13 of page 19). Thus the derivatives disclosed by Valenta et al. comprise "reduced allergenic activity" of 25% or less as compared to the native allergen as per the definition set forth on page 4 of the instant specification.

The derivatives of Valenta et al. are taught to be used for specific hyposensitization therapy in mammals, especially humans, wherein hyposensitization involves the generation of an IgG immune response that binds the native allergen (see particularly the paragraph spanning pages 5 and 6). Valenta et al. do not explicitly state that the IgG response that is achieved as part of their hyposensistization methods is an IgE-blocking antibody response, although they do teach that these fragments comprise epitopes known to be bound by monoclonal antibodies that inhibit the binding of allergic patient IgE to native Bet v 1 (see particularly lines 20-34 of page 15). However, it is inherent that an immune response which precludes binding of IgE to the native allergen occurs upon administration of the Bet v 1 derivatives disclosed by Valenta et al. This is because Vrtala et al. teach that administration of the same derivatives as taught by Valenta et al. induce a blocking antibody response (see entire document, particularly the abstract, discussion, and Tables II and III). Further, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." Note

that the induction of an IgE-blocking response is a scientific explanation for why the derivatives of Valenta et al. are effective in methods of immunotherapy.

Additionally, claims 53 and 54 are included in this rejection because Example 3 of Valenta et al. discloses that the Bet v 1 fragments used in their example are the Bet v 1 fragments disclosed by Vrtala et al. in their 1997 J. Clin. Invest. paper. As was discussed above in conjunction with the teachings of Vrtala et al., it appears that the recitation of amino acids 1-73 and 74-159 in the instant specification is a typographical error. This is because the instant specification teaches the '97 Vrtala et al. paper as the source of the peptides used in the examples of the instant specification and the '97 reference clearly teaches fragments 1-74 and 75-160 of Bet v 1 rather than fragments 1-73 and 74-159 of Bet v 1.

Therefore, the prior art anticipates the instant invention.

Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant's argues that Valenta et al. have not "enabilingly disclosed the periodicity element of claim 33 and its dependent claims".

This argument is not persuasive. The only "periodicity element" of the instant rejected claims is found in claim 33 which recites "comprising periodically administering for a number of times". The paragraph spanning pages 5 and 6 of Valenta et al. discloses:

> The second aspect of the invention is specific hyposensitization therapy. This therapy may be performed as known in the art for protein allergens and encompasses administering repeatedly to the mammal, typically a human individual, suffering from type I allergy against the protein allergen an immunogen that is capable of raising as IgG immune response against the protein allergen. Administration may be done systemically, for instance by injection, infusion, etc., but also the oral route has been suggested in order to expose the intestinal part of the immune system. The immunogen may be admixed with suitable adjuvants such as aluminium oxide. See further Norman P S, "Current status of immunotherapy for allergies and anaphylactic reactions" Adv.Internal. Medicine 41 (1996)681 713.

Given that the allergen is administered repeatedly (i.e. multiple times), said administrations must occur over an interval of time, thus providing a "periodicity element". Further, the art of Norman cited by Valenta et al. teaches that it is known in the art that administrations are repeatedly given over a period of time, often years (see entire document, particularly pages 681 and 698).

It is also noted that applicant has not commented upon the inclusion of claims 53 and 54 in the instant rejection as part of the reply received January 29, 2007. As such, it appears that applicant agrees that the examiner's analysis is correct and that the discrepancy in Bet v 1 fragment lengths is due to a typographical error in the instant specification.

12. Claims 33, 49, and 50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, see entire document) in view of Hem et al. (chapter 9 of Vaccine Design: The Subunit and Adjuvant Approach, 1995, pages 249-76, see entire document) for the reasons of record.

The office action mailed June 20, 2006 states:

> The teachings of Vrtala et al. have been discussed above. While Vrtala et al. teach that their allergen derivatives are to be used in methods of human administration (see entire document, particularly the abstract and discussion sections), these teachings differ from the instant claimed invention in that they do not teach the use of aluminum hydroxide as part of the administered composition.
>
> Hem et al. teach that aluminum hydroxide is a widely used adjuvant that offers the important advantage of being the only adjuvant licensed by the Food and Drug Administration for administration to human patients (see entire document, particularly the introduction).
>
> Therefore, it would have been obvious at the time the invention was made to substitute aluminum hydroxide for the adjuvant used in the methods of administration taught by Vrtala et al. Motivation to make this substitution comes from the teachings of Vrtala et al. that their allergen derivative compositions are to be administered to humans and the teachings of Hem et al. that the only adjuvant that can be administered to human patients is aluminum hydroxide.

Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant argues that there is no motivation to combine because immunotherapeutic agents, such as Bet v 1 fragments, are not the same as vaccines.

This argument is not persuasive because it is well known in the art that immunotherapeutic agents are used for vaccination, as is evidenced by the teachings of

Bystryn (see entire document, particularly the abstract). Further, the title of the instant application is "Allergy vaccines".

Applicant also repeats arguments concerning the lack of a "periodicity element".

This argument is not persuasive, has been discussed above, and will not be addressed further.

13. Claims 33, 38, and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, of record, see entire document) for the reasons of record.

The office action mailed June 20, 2006 states:

> The teachings of Vrtala et al. have been discussed above. These teachings differ from the instant claimed method in that while Vrtala et al. teach repeated administration of allergen derivatives wherein the period between administrations is at least 14 days, Vrtala et al. do not teach that the time interval between the third and fourth administrations is longer than the time interval between the first three administrations. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made modify the interval between administrations. As person of ordinary skill in the art at the time the invention was made would have been motivated modify the time intervals to optimize the treatment method, and determining the optimal intervals of administration of the allergen derivative is well within the purview of one of ordinary skill in the art at the time the invention was made. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II A.

Applicant's arguments filed January 29, 2007 have been fully considered but they are not persuasive. Applicant argues that the examiner has engaged in hindsight reasoning to reject the claims.

This argument is not persuasive. Vrtala et al. disclose that a blocking antibody response can be obtained in a patient subsequent to monthly administrations of their Bet v 1 fragments. As such, the general conditions of the claims (i.e. periodic administration wherein the period between administrations is greater than 14 days) are taught in the art and *In re Aller* held that when such general conditions are known, optimizing involves only routine skill in the art. Applicant states in the reply that only routine skill is involved ("Applicants understand that a simple and elegant screening procedure of this invention involves routine skill in the art...") but then states that the exact timing and dosages are not obvious. As stated in the rejection of record, a skilled artisan would be motivated to optimize the protocol of Vrtala et al., and given that such optimization is routine and thus within the skill of an ordinary artisan, the claimed

method is obvious. Applicant has supplied only argument, not evidence, to rebut the obviousness rejection of the instant claims. As was discussed supra and as is discussed in MPEP 2145, attorney argument does not replace the need for evidence when rebutting cases of prima facie obviousness.

14. Claims 33, 38-41, and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valenta et al. (WO 99/16467 A1, of record, see entire document).

The teachings of Valenta et al. have been discussed above. These teachings differ from the instant claimed method in that while Valenta et al. teach repeated administration of allergen derivatives, Valenta et al. do not teach specific administration timings or dosage amounts. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made modify the treatment methods of Valenta et al. given that it is well within the purview of skilled artisans to determine suitable dosages and timings for the treatment of their patients. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II A. As such, specific dosages and timings of administered agents do not generally impart novelty or nonobviousness to a claimed invention, especially in the absence of evidence to the contrary. Note that there does not appear to be any evidence of record to indicate that the recited dosages and timings are not obvious and could not be obtained by routine optimization.

15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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